REMARKS

Pending claims

Claims 25-35 and 67-79 are pending. Claims 1-24, 36-66 and 80-127 have been cancelled without prejudice as relating to a non-elected invention. New claims 128-149 have been added as suggested by the Examiner in the November 17, 2003 Office Action. Support for the new claims are found through the specification. No new matter is added by this response.

Applicants wish to thank Examiner Bunner for the courtesy extended to their attorneys during a telephonic interview on February 12, 2004. Applicants believe that the interview was helpful and productive, the essence of which is summarized below. As per our telephone conversation with the Examiner, Applicants are including 1) a copy of a manuscript of the inventor (Exhibit A) demonstrating reduction to practice of the transplantation methods of the invention, in the absence of transplant rejection; and 2) exhibits B-G demonstrating successful xenotransplantation into a human.

Rejection of Claims 25-35 and 67-79 under 35 U.S.C. §112, first paragraph

Claims 25-35 and 67-79 are rejected under 35 U.S.C. §112, first paragraph for alleged lack of adequate written description and enablement.

The Examiner asserts that although the specification is enabling for the methods of treatment (as claimed in claims 25-35), wherein an isolated nestin-positive pancreatic stem cell from a pancreatic islet of a human donor is transferred into a non-human or human subject with diabetes mellitus, the specification is not enabling for the analogous method wherein an isolated nestin-positive pancreatic stem cell from a pancreatic islet is transferred into a patient with diabetes mellitus. The Examiner also asserts that although the specification is enabling for the claimed methods of transplantation (as claimed in claims 67-79), wherein an isolated nestin-positive pancreatic stem cell from a pancreatic islet of a human donor is transferred into a non-human or human animal, the specification is not enabling for an analogous method of transplantation wherein an isolated nestin-positive pancreatic stem cell from a pancreatic islet of

a donor is transferred into a mammal.

In particular, the Examiner states at page 5 that "the state of the art is such that patients may suffer one of two types of graft or transplant rejections, host-versus-graft rejection or graft-versus-host rejection (GvHR)." The Examiner states further at page 6 that "the skilled artisan cannot predict that the differentiated pseudo-islet like aggregates can be successfully immunologically transplanted into the recipient patient/animal."

Applicants respectfully disagree.

Applicants submit that the specification of the instant application teaches that nestin-positive islet-derived stem/progenitor cells (NIPS) can be successfully engrafted in immunocompetent animals without a requirement for immunosuppression. Example 10 of the instant application (page 56, line 22 through page 58, line 3) teaches successful xenogeneic transplantation of human NIPS into mice that were not immunosuppressed. The specification states at page 56, line 26- page 57, line 3 "[t]he transplanted human cells were not rejected by the mouse recipient. Current understanding is that a xenograft, such as human tissue, would be rejected by the mouse within 5-10 days. Contrary to current understanding, we found that in 8 of the 8 non-immunosuppresed mice tested to date, all of the transplants successfully engrafted and proliferated into large masses of tissue engulfing the pole of the kidney by one month (30-38 days) after a transplantation..."

Also, attached hereto is a manuscript from the inventor (Exhibit A), currently in press in the American Journal of Pathology that describes the successful engraftment of pancreatic islet-derived progenitor cells in immunocompetent recipients. The manuscript teaches that nestin-positive islet-derived stem/progenitor cells (NIPs), prepared from human adult pancreata survive engraftment and produce tissue chimerism when transplanted into immunocompetent mice either under the kidney capsule or by systemic injection. The manuscript also teaches that nestin-positive cells in rat pancreatic islets do not express either class I or class II major histocompatibility (MHC) antigens. The manuscript states at page 15, "our findings of xenoengraftment of the human NIPs transplanted under the kidney capsules, or by intravenous injection into the systemic circulation, of non-immunosuppressed mice (the cells grow and are

not rejected by the usual criteria of a rapid, vigorous rejection of a xenograft) manifest a property of stem-like progenitor cells as they appear to induce immune tolerance and thereby resist host vs. graft rejection."

As suggested by the Examiner during the February 12, 2004 Examiner interview, Applicants have also attached hereto publications demonstrating successful xenotransplantion into a human recipient.

U.S. 6,090,400 (filed June 17, 1996, Issued July 18, 2000, Exhibit B) and U.S. 6,146,653 (filed December 11, 1998, Issued November 14, 2000, Exhibit C) teach xenotransplantation of pig islet cells into human subjects. These patents state at column 8, line 29 through line 63 ('400) and column 7, line 54 through column 8, line 18 ('653):

> "Two such xenotransplants have been carried out in diabetic human subjects. The first was a 15 year old female who had diabetes for 7 years requiring the injection of daily dose of insulin totaling 76-78 units/day. Despite this, her diabetic blood glucose levels were poorly controlled. The Xenotransplant was carried out as above, using 200,000 islets. There was an immediate reduction in insulin requirement which reached its maximum between the 16-21st day post operatively. During this period average blood glucose control was better than preoperatively. This reduction averaged 18 less than the pretransplant dose during this period. The effect slowly waned over the next few weeks.
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> The second transplant involved a 15 year old diabetic male who had the disease for 7 years. On this occasion 800,000 viable islets of more than 150 μ in diameter were transplanted. On this occasion, the insulin dose was reduced to a minimum of 55% of the pretransplant dose in the third week post transplant and averages 62% of the pretransplant dose in the fifth week after transplantation. The average blood glucose levels before transplantation of about 10 mm/1 have been reduced to 6.5 mm/1 in the 4th and 5th weeks. The time course of blood glucose and insulin dose in this subject are shown in FIG. 1.
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> It appears that the transplanted piglet islets are capable of producing insulin for at least 5 weeks after engraftment in diabetic humans and that the magnitude of the effect is related to the number of islets implanted. The duration of the effect in the second instance indicates that acute rejection of the transplanted tissue has not occurred. No side effects of the procedure have been encountered. Further transplant procedures will be carried out using a larger number of islets but in other ways not varying the technique. To date the results in humans are similar to those described in the diabetic mice transplanted with piglet islets.

> The reduction in daily insulin dose relative to the pretransplant level is plotted against the days after transplantation. Note FIG. 2. There is a maximum response of 40% reduction and a maximum duration of three months. Porcine C-peptide was detected in all sera taken at the time of reduction in insulin dose was greater than 10%, i.e., the reduction is likely to be the result of pig insulin secretion by the transplant. The least response was obtained with the small dose of islets."

Also attached hereto is a post-filing publication (Schumacher et al., 2000, Neurology, 54:1042-1050, Exhibit D) that describes transplantation of porcine embryonic ventral mesencephalic cells into human patients with Parkinson's disease. This publication reports the 1 year follow-up data of the first implantation of xenogeneic neural tissue into humans. Schumacher et al. states at page 1046 that "[u]nilateral implantation of a suspension of 12 million porcine embryonic VM cells into the striatum of patients with PD was well tolerated. There were no serious adverse effects directly related to the implantation of porcine embryonic cells, and no evidence of transmission of porcine-derived pathogens or a porcine-specific endogenous retrovirus."

U.S. 2001/0049827 A1 (Exhibit E, Filed August 4, 1997, Published December 6, 2001) discloses successful implantation of porcine fetal neuronal cells from pathogen-free fetal pigs into patients with Parkinson's disease. This patent application states at page 8 through page 9 (paragraph 0109) that "[c]linical studies of fetal porcine neuronal cell transplantation into patients suffering severe Parkinson's disease were conducted as described above. To date, four patients have been transplanted of the 12-patient study. The first three transplant recipients received cyclosporin, while the fourth recipient received transplanted neuronal cells treated to prevent rejection. All four recipients have exhibited positive results, and the first patient's seven month evaluation exhibited significant improvement in PET scan results."

Also attached is Reemtsma et al., 1964, Annals of Surgery, 160: 384-410 (Exhibit F). This publication teaches successful xenotransplantation of a chimpanzee kidney into a human (see pages 392-394, Case 3).

The Starzl et al. 1993, The Lancet, 341:65-71 reference (also attached, Exhibit G) discloses successful baboon to human liver xenotransplantation.

In view of all of the above, Applicants request that the rejection be reconsidered and withdrawn.

Rejection of Claims 25, 28-30 and 35 for Obviousness-type Double Patenting

Claims 25, 28-30 and 35 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13 and 15-18 of copending Application No. 09/731,261 and claims 19 and 24-27 of copending Application No. 09/963,875. The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other.

In response to this rejection, Applicants submit that they will submit a terminal disclaimer to disclaim any portion of a patent issuing from the present application which would extend beyond the term of a patent issuing from the 09/731,261 and 09/963,875 applications, upon notification of allowable claims in the present application.

Rejection of Claims 67-68, 72-74 and 79 for Obviousness-type Double Patenting

Claims 67-68, 72-74, and 79 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-18 of copending Application No. 09/731,261 and claims 19 and 23-27 of copending Application No. 09/963,875. The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other.

In response to this rejection, Applicants submit that they will submit a terminal disclaimer to disclaim any portion of a patent issuing from the present application which would extend beyond the term of a patent issuing from the 09/731,261 and 09/963,875 applications, upon notification of allowable claims in the present application.

CONCLUSION

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,

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